PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 12320640/EJH/ar	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU2003/001078**	International Filing Date *(day/month/year)* 22 August 2003	Priority Date *(day/month/year)* 23 August 2002
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] A01K 67/00, C12N 15/09, C12N 15/63, A61K 38/19, A61K 48/00, A61K 39/395, A61P 29/00		
Applicant THE WALTER AND ELIZA HALL INSTITUTE OF MEDICAL RESEARCH et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of **5** sheet(s).

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [X] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand 2 March 2004	Date of completion of the report 2 July 2004
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer Arati Sardana **ARATI SARDANA** Telephone No. (02) 6283 2627

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001078

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1-49** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **50-54** received on **21 June 2004** with the letter of **16 June 2004**

☒ the drawings, pages **1/16-16/16** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims **1-45**	**YES**
	Claims	**NO**
Inventive step (IS)	Claims **1-45**	**YES**
	Claims	**NO**
Industrial applicability (IA)	Claims **1-45**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

CITATIONS:

D1: US 5,420,109 A

D2: US 5,639,455 A

D3: US 2002/0141994 A

D4: Ghivizzani Steven C. et al. "Gene therapy approaches for treating rheumatoid arthritis" ***Clinical Orthopaedics and Related Research, (October 2000), (379 Suppl) pg. S288-99 Ref: 50.***

D5: Saggio I.et al. "Adenovirus-mediated gene transfer of a human Il-6 antagonist" ***Gene Therapy, Vol. 4, No. 8, (August 1997), pg. 839-845.***

D6: Campbell Ian K.et al. "The colony-stimulating factors and collagen-induced arthritis: exacerbation of disease by M-CSF and G-CSF and requirement for endogenous M-CSF ***Journal of Leukocyte Biology, Vol. 68, No. 1, (July 2000), pg. 144-50.***

D7: Roessler Blake J. et al. "Inhibition of Interleukin-1-Induced Effects in Synoviocytes Transduced with the Human IL-1 Receptor Antagonist cDNA Using an Adenoviral Vector" *HUMAN GENE THERAPY, Vol. 6, No. 3, (March 1995), pg. 307-16.*

D8: Bernard L. A. et al. "Pimecrolimus 1% cream (Elidel) for atopic dermatitis" *Skin Therapy Letter, Vol. 7, No. 4, (April 2002), pg. 1-3.*

D9: Kawamura Hiroki. et al. " Expansion of Extrathymic T cells as well as Granulocytes in the liver and other organs of Granulocyte-colony Stimulating Factor Transgenic Mice: Why They Lost the Ability of Hybrid Resistance" *The Journal of Immunology, Vol. 162, No. 10, (15 May 1999), pg. 5957-64*

D10: Hermans M. H. et al. "Sustained Receptor Activation and Hyperproliferation in Response to Granulocyte Colony-stimulating Factor (G-CSF) in Mice with a Severe Congenital Neutropenia/Acute Myeloid Leukemia-derived Mutation in the G-CSF Receptor Gene" *Journal of Experimental Medicine, Vol. 189, No. 4, (15 February 1999), pg. 683-92*

EXPLANATION:

D3 was published after the priority date of the present application and therefore do not constitute prior art for the purpose of articles 33(2) and 33(3) of the PCT. See however the indication in Box VI.

Continued in Supplemental Box I

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
US 2002/0141994	03 October 2002	23 February 2001	20 March 2000

D3 discloses treating inflammatory diseases such as rheumatoid arthritis by administering an inhibitor of colony stimulating factor (csf) or an agent that inhibits the binding of csf to a csf receptor. Wherein the inhibitor or the agent that inhibits the binding of csf to csf receptor is a monoclonal antibody that binds to csf or csfr, an antagonist of csfr and an agent that inhibits the expression of csf. It further discloses pharmaceutical preparations of such inhibitors and screening assays for identifying agents that inhibit or otherwise hinder the binding of a csf to a csf receptor. Also disclosed in the above document are knockout csf or csfr mice.

The above disclosure deprives claims 1-42 of their novelty.

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

International application No.
PCT/AU2003/001078

Supplemental Box I

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of BOX V

The disclosure of D1, D2 and D4-D10 does not deprive amended claims 1-45 filed on 21 June 2004 of their novelty or inventive step. Therefore claims 1-45 are novel and inventive.

CLAIMS:

1. A method for the treatment or prophylaxis of an inflammatory condition in a subject, said method comprising administering to the subject an effective amount of an agent which inhibits the activity of an inflammatory cytokine or its receptor and/or which reduces the level of expression of a gene encoding said inflammatory cytokine or its receptor.

2. The method of claim 1 wherein the inflammatory cytokine is granulocyte-colony stimulating factor (G-CSF) or a functional or structural homolg thereof.

3. The method of claim 1 or 2 wherein the receptor is the granulocyte-colony stimulating factor receptor (G-CSFR) or a structural or functional homolog thereof.

4. The method of any one of claims 1 to 3 wherein the inflammatory condition is arthritis or a symptomatically related disease.

5. The method of claim 4 wherein the condition is rheumatoid arthritis (RA).

6. The method of claim 4 wherein the condition is collagen induced arthritis (CIA).

7. The method of any one of claim 1 wherein the subject is an animal or avian species.

8. The method of claim 7 wherein the animal is a mammal.

9. The method of claim 8 wherein the mammal is a primate.

10. The method of claim 9 wherein the primate is a human.

11. The method of claim 8 wherein the mammal is a rodent.

12. The method of claim 11 wherein the rodent is a mouse.

13. The method of any one of claim 1 wherein the agent is an antibody raised against the cytokine or its receptor.

14. The method of claim 13 wherein the agent is an antibody raised against G-CSF, G-CSFR or parts or immunological relatives thereof.

15. The method of claim 13 or 14 wherein the antibody is a monoclonal antibody.

16. The method of claim13 or 14wherein the antibody is a polyclonal antibody.

17. The method of claim 1 wherein the agent is soluble G-CSFR or a functional homolog, analog or derivative thereof.

18. The method of claim 1 wherein the agent is a chemical analog of G-CSF.

19. The method of claim 1 wherein the agent is a chemical analog of G-CSFR.

20. The method of any one of claims 17 to 19 wherein the agent is a protein.

21. The method of claim 1 wherein the agent is a nucleic acid.

22. The method of claim 21 wherein the nucleic acid is DNA or RNA and comprises a sense or antisense polynucleotide sequence or a genetic sequence encoding G-CSF or G-CSFR or part or transcript thereof.

23. A method for identifying an agent which inhibits the activity of an inflammatory cytokine or its receptor, said method comprising contacting putative inhibitory agents with said inflammatory cytokine or its receptor, wherein the agent is identified as an inhibitory agent by binding or otherwise associating with said cytokine or cytokine receptor.

24. A method for identifying an agent which which regulates the expression of a genetic sequence encoding an inflammatory cytokine or its receptor, said method comprising contacting putative regulatory agents with said genetic sequence encoding an inflammatory cytokine or its receptor, wherein the agent is identified as a regulatory agent by binding or otherwise associating with said genetic sequence encoding a cytokine or cytokine receptor.

25. The method of claim 23 or 24 wherein the inflammatory cytokine is G-GSF or a functional or structural homolog thereof.

26. The method of claim 23 or 24 wherein the receptor is G-CSFR or a functional or structural homolog thereof.

27. The method of claim 24 wherein the genetic sequence is a genetic sequence comprising exons and/or introns encoding G-CSF or a genetic sequence comprising exons and/or introns encoding G-CSFR, or a promoter or enhancer region thereof.

28. A pharmaceutical composition comprising an agent which inhibits the activity of an inflammatory cytokine or its receptor in a subject and/or which reduces the level of expression of the gene encoding said inflammatory cytokine or its receptor in a subject, together with a pharmaceutically acceptable carrier or diluent.

29. The pharmaceutical composition of claim 28 wherein the inflammatory cytokine is granulocyte-colony stimulating factor (G-CSF) or a functional or structural homolg thereof.

30. The pharmaceutical composition of claim 28 or 29 wherein the receptor is the granulocyte-colony stimulating factor receptor (G-CSFR) or a structural or functional homolog thereof.

31. The pharmaceutical composition of any one of claims 28 to 30 wherein the inflammatory condition is arthritis or a symptomatically related disease.

32. The pharmaceutical composition of claim 31 wherein the condition is rheumatoid arthritis (RA).

33. The pharmaceutical composition of claim 32 wherein the condition is collagen induced arthritis (CIA).

34. The pharmaceutical composition of claim 28 wherein the subject is an animal or avian species.

35. The pharmaceutical composition of claim 34 wherein the animal is a mammal.

36. The pharmaceutical composition of claim 35 wherein the mammal is a primate.

37. The pharmaceutical composition of claim 36 wherein the primate is a human.

38. The pharmaceutical composition of claim 34 wherein the mammal is a rodent.

39. The pharmaceutical composition of claim 38 wherein the rodent is a mouse.

40. The pharmaceutical composition of claim 28 wherein the agent is an antibody raised against the cytokine or its receptor.

41. The pharmaceutical composition of claim 40 wherein the agent is an antibody raised against G-CSF, G-CSFR or parts or immunological relatives thereof.

42. The pharmaceutical composition of claim 40 or 41 wherein the antibody is a monoclonal antibody.

43. The pharmaceutical composition of claim 40 or 41 wherein the antibody is a polyclonal antibody.

44. The pharmaceutical composition of claim 28 wherein the agent is soluble G-CSFR or a functional homolog, analog or derivative thereof.

45. The pharmaceutical composition of claim 28 wherein the agent is a chemical analog of G-CSF.

46. The pharmaceutical composition of claim 28 wherein the agent is a chemical analog of G-CSFR.

47. The pharmaceutical composition of any one of claims 44 to 46 wherein the agent is a protein.

48. The pharmaceutical composition of claim 28 wherein the agent is a nucleic acid.

49. The pharmaceutical composition of claim 48 wherein the nucleic acid is DNA or RNA and comprises a sense or antisense polynucleotide sequence or a genetic sequence encoding G-CSF or G-CSFR or part or transcript thereof.

50. A vector comprising a genetic sequence encoding the agent recited in any one of claims 20 to 22, wherein said genetic sequence is operably connected to an animal-operable promoter sequence.

51. An animal cell comprising the vector of claim 50.

52. An animal comprising the cell of claim 51.

53. The animal or cell thereof of claims 51 or 52 wherein said animal or cell thereof is a mouse or mouse cell.

54. The animal or cell thereof of claims 51 or 52 wherein said animal or cell thereof is a human or human cell.

55. A targetting or marker-exchange mutagenesis vector useful for inactivating a gene encoding G-CSF or G-CSFR in a cell, said vector comprising two segments of genetic material encoding G-CSF or G-CSFR, or fragments thereof, flanking a positive or negative selectable marker.

56. A genetically modified animal cell comprising the vector of claim 30 or part of said vector.

57. The genetically modified cell of claim 30 or 31 wherein said cell is an embryonic stem cell.

58. A genetically modified animal or embryo comprising, or being derived from, one or more of the cells of claims 31 or 32, wherein said animal produces low amounts of G-CSF or G-CSFR relative to a non-gentically modified animal of the same species.

59. The genetically modified animal of claim 33 or the cell of claims 31 or 32 wherein the animal is a mouse.

60. The genetically modified animal of claim 33 or the cell of claims 31 or 32 wherein the animal is a human.

Rec'd PCT/PTO 23 FEB 2005
PCT/AU2003/001078

61. A method of producing the genetically modified cell of claim 31 or 32, said method comprising introducing the vector of claim 30 into one or more embryonic stem (ES) cell(s) and selecting for expression of the selectable marker gene, wherein the G-CSF and/or G-CSFR gene in the resultant transformed cell(s) is inactivated by homologous recombination with said vector.

62. An *in-vivo* method for identifying agents capable of inhibiting the activity of G-CSF and/or inhibiting the interaction of G-CSF with G-CSFR and thereby ameliorate the effects of inflammation, said method comprising administering a putative inhibitory agent to the animal of any one of claims 33 to 35, wherein said agent is identified as having interactivity with G-CSF or G-CSFR by the agent having a detectable physiological effect in a wild type animal of the same species, but a reduced effect in the animal of any one of claims 33 to 35 which exhibits reduced expression of G-CSF and/or G-CSFR.